REMARKS

Applicants have amended their claims in order to further clarify the definition of various aspects of the present invention. Specifically, each of claims 18, 42 and 43, the independent claims being considered on the merits in the above-identified application, has been amended to further clarify that each of the protein/phospholipid complex and the protein hydrolyzate/phospholipid complex contains 20-50 wt% of bound phospholipid, and that the bound phospholipid in the complex is a phospholipid which remains bound to the protein or protein hydrolyzate after being treated with a nonpolar organic solvent. In connection with this amendment of claims 18, 42 and 43, note, for example, the paragraph bridging pages 2 and 3 of Applicants' specification.

Initially, it is respectfully requested that the present amendments be entered. It is respectfully submitted that the present amendments clarify the nature of the complex, previously argued in the present application, and clarify the complex that includes the specified amount of bound phospholipid, as previously argued, and do not raise any new issues, including any issue of new matter. In addition, by further defining the complex, it is respectfully submitted that the present amendments clearly materially limit issues remaining in connection with the above-identified application. Noting in particular questions raised by the Examiner in connection with the complex, set forth, for example, in the paragraph bridging pages 3 and 4 of the Office Action mailed February 20, 2004, is respectfully submitted that the present amendments clearly materially limit issues remaining in connection with the above-identified application; and at the very least present the claims in better form for appeal. Noting contentions by the Examiner in connection with the prior art

rejections, made in the aforementioned Office Action mailed February 20,2004, it is respectfully submitted that the present amendments are clearly timely.

In view of the foregoing, it is respectfully submitted that Applicants have made the necessary showing under 37 CFR § 1.116(c); and that, accordingly, entry of the present amendments is clearly proper.

Applicants respectfully submit that all of the claims presented for consideration on the merits by the Examiner patentably distinguish over the teachings of the references applied by the Examiner in rejecting claims in the Office Action mailed February 20, 2004, that is, the teachings of the publications by Sugano, et al., "Cholesterol-Lowering Activity Of Various Undigested Fractions Of Soybean Protein In Rats", in J. Nutr. (1990), pages 977-85; Sugano, et al. "The Hypocholesterolemic Action of the Undigested Fraction of Soybean Protein in Rats", in Atherosclerosis, 72 (1988), pages 115-122; Imaizumi, et al., "Influence of Saturated and Polyunsaturated Egg Yolk Phospholipids on Hyperlipidemia in Rats", Agric. Biol. Chem., 53 (9), 1989, pages 2469-74; Sirtori, et al., "Cholesterol-Lowering and HDL-Raising Properties of Lecithinated Soy Proteins in Type II Hyperlipidemic Patients", in Ann. Nutr. Metab. 29 (1985), pages 348-357; and Williams, et al., "Intravenously Administered Lecithin Liposomes: A Synthetic Antiatherogenic Lipid Particle", in Perspectives in Biology and Medicine, 27 (3), 1984, pages 417-431, under the provisions of 35 U.S.C. § 103.

It is respectfully submitted that these references as applied by the Examiner would have neither taught nor would have suggested such a method for improving the cholesterol metabolism of an animal, including administering a protein/ phospholipid complex or protein hydrolyzate/ phospholipid complex, each containing

20-50 wt% of bound phospholipid, the protein being soybean protein, and wherein the bound phospholipid in the complex is a phospholipid which remains bound to the protein or protein hydrolyzate after being treated with a nonpolar organic solvent. See claim 18.

It is further respectfully submitted that these applied references would have neither disclosed nor would have suggested a method for lowering cholesterol or lipid level of an animal, or for producing food or feed, which includes administering or adding to a food or feed material, the protein/phospholipid complex or protein hydrolyzate/phospholipid complex as referred to previously in connection with claim 18. Note claims 42 and 43.

Furthermore, it is respectfully submitted that the teachings of these applied references would have neither disclosed nor would have suggested the other aspects of the present invention as in the remaining, dependent claims being considered on the merits in the above-identified application, including (but not limited to) wherein the phospholipid is lecithin (see claims 35, 44 and 47), or wherein the phospholipid is enzyme-modified lecithin obtainable by treating lecithin with phospholipase (see claims 36, 45 and 48); and/or wherein the animal to which the complex is administered is human (see claims 38 and 46).

The present invention is directed to decreasing cholesterol concentration in blood and in the liver.

In recent years, mortality from adult diseases, particularly cardiovascular disorders, is rapidly rising, and a correlation between occurrence of such disorders and cholesterol concentration in blood has been pointed out. Attempts have been made to lower the cholesterol concentration in blood by the use of specific food

components, for example, various proteins such as soybean protein or soybean protein hydrolyzate; or, in other proposals, by the use of egg yolk phospholipid. See page 1, lines 15-30 of Applicants' application.

Attempts have also been made to lower cholesterol concentration in blood by use of a combination of lactalbumin, collagen, soybean protein, or wheat gluten, and soybean lecithin, or by the use of a textured soybean protein containing 6% of soybean lecithin. Note the paragraph bridging pages 1 and 2, and the first full paragraph on page 2, of Applicants' specification

However, these prior techniques do not provide desired level of cholesterol reduction.

Against this background, Applicants provide a material providing unexpectedly better cholesterol reduction in the blood and in the liver. Applicants have found that by using a complex of a protein/phospholipid or protein hydrolyzate/phospholipid, containing 20-50 wt% of bound phospholipid in the complex, unexpectedly better reduction of cholesterol is achieved. As to what is meant by the complex having bound phospholipid, attention is respectfully directed to the paragraph bridging pages 2 and 3 of Applicants' specification, wherein the term "bound phospholipid" is defined as a phospholipid which remains bound to a protein after being treated with a nonpolar organic solvent, such as petroleum ether.

As seen in the evidence of record, the complex as defined in the present claims, having 20-50 wt% bound phospholipid to the protein, achieves unexpectedly better results in reduced cholesterol in the blood and in the liver, as compared, inter alia, to material containing mixtures of protein and phospholipid (that is, a mixture of

the substances, and not wherein the phospholipid is bound to the protein or protein hydrolyzate).

As for the evidence of unexpectedly better results, attention is respectfully directed to Table 2 on page 9 of Applicants' specification, together with the description of the four groups at the top of page 9. Note that Test Groups 3 and 4 showed higher arteriosclerosis index as compared with Test Groups 1 and 2, which indicates that the cholesterol metabolism in serum (e.g., blood) was improved in Test Groups 3 and 4. Test Groups 3 and 4 also showed lower total cholesterol concentration in liver as compared with Test Groups 1 and 2. Note page 10, lines 1-15 of Applicants' specification.

Note also Table 4, showing results using Test Groups 5 and 6, with Groups 5 and 6 being defined on page 11, lines 5-12. As shown in Table 4, Test Group 6 was equal to Test Group 5 in arteriosclerosis index, but showed lower total cholesterol concentration in liver. Note, similarly, Tables 6 on page 13 of Applicants' specification, with the test groups for Table 6 being described from page 12, line 16 to page 13, line 7. As can be seen in each of these test groups, the materials having bound phospholipid content which is relatively high, as compared with compositions having a bound phospholipid content which is relatively low, even where the compositions are a mixture having a relatively large unbound phospholipid content, have unexpectedly better results in reduced cholesterol in the blood and/or liver.

Attention is also directed to the Declarations under 37 CFR § 1.132 submitted in the above-identified application, with the Amendments filed March 11, 2002, and December 2, 2002. As seen in Fig. 1 of the Declaration of G. Hori submitted March 11, 2002, the protein/phospholipid complex containing 20-50 wt% bound

phospholipid demonstrated the maximum IC_{50} level, that is, provides unexpectedly improved cholesterol metabolism, as compared with less than 20 wt% bound phospholipid (for example, 10% bound phospholipid).

The Declaration of S. Nagaoka submitted with the Amendment filed March 11, 2002 shows, in Table 2 on page 6 and Table 4 on page 10, that contents of, inter alia, cholesterol in the serum and liver of groups tested with materials within the scope of the present claims were lower than those of soy protein-fed groups.

Attention is also directed to the Declaration of M. Takada submitted with the Amendment of December 2, 2002 in the above-identified application, and in particular to the results shown in Figs. 1 and 2 on page 4 and Figs. 3 and 4 on page 7 of this Declaration. As seen in Figs. 1 and 2, contents of serum total cholesterol and cholesterol in the liver were decreased with increased amount of phospholipid in soy protein/phospholipid complexes; and there were significant differences in content of liver cholesterol between soy protein with 20% bound phospholipid as compared with soy protein itself and a mixture of soy protein and phospholipid. Note, in particular, Fig. 4, showing cholesterol in the liver, with much less cholesterol being seen in groups fed with diets containing soy protein with 20% bound phospholipid, as compared with soy protein mixed with 20% phospholipid.

Clearly, this evidence of record establishes unexpectedly better results achieved according to the present invention utilizing the complex of soy protein and phospholipid, containing 20-50 wt% of bound phospholipid.

On page 6 of the Office Action mailed February 20, 2004, the Examiner has addressed Applicants' arguments based on the "Declaration"; it is respectfully submitted that all of the three Declarations must be considered, as well as the

evidence in Applicants' specification. See In re DeBlauwe, 222 USPQ 191 (CAFC 1984). Taking all of the evidence of record into consideration, it is respectfully submitted that this evidence clearly establishes unexpectedly better results achieved for the use of the complexes with amounts of bound phospholipid as in the present claims, as compared with the prior art.

In addition, the contention by the Examiner that the figures show no cholesterol values for soy protein by itself and lecithin by itself, in order to assess the synergistic effect, is noted. It is respectfully submitted that Applicants have tested even closer compositions (that is, mixtures of soybean protein and phospholipid) to materials used according to the present invention, than that of the soy protein by itself and lecithin by itself. See Manual of Patent Examining Procedure 716.02(e). It is respectfully submitted that the evidence of record clearly establishes unexpectedly better results for complexes having an amount of bound phospholipid, as in the present claims, as compared with the closest prior art.

The contention by the Examiner on page 6 of the Office Action mailed February 20, 2004, that studies were performed with only soybean protein and not with hydrolyzates or wheat protein, is noted. Reference to wheat protein is not understood, since wheat protein is not in the present claims.

The Examiner also alleges that the studies are not commensurate with the scope of the claims in terms of enzyme modified phospholipids or lecithin. However, it is respectfully submitted that the performed studies provide evidence which one of ordinary skill in the art would accept as establishing unexpectedly better results for use of materials commensurate with the scope of the present claims.

For example, as contended in the remarks of the Amendment filed

November 7, 2003, that since protein hydrolyzate is one of the proteins, and enzyme-modified lecithin is one of the phospholipids, protein/phospholipid complex, protein/enzyme-modified phospholipid complex, protein hydrolyzate/phospholipid complex and protein hydrolyzate/enzyme-modified phospholipid complex have the significant effect on improving cholesterol metabolism similarly. As shown in Group 4 of Test Example 1, Group 6 of Test Example 2, and Group 9 of Test Example 3 of the present specification, and in the previously referred to Declaration of S. Nagaoka, the cholesterol metabolism-improving effects of protein/enzyme-modified phospholipid complex, protein hydrolyzate/phospholipid complex and protein hydrolyzate/enzyme-modified phospholipid complex containing 20 wt% of bound phospholipid or enzyme-modified phospholipid are the same or more than the protein/phospholipid complex containing 20 wt% of bound phospholipid. The significant effect of protein/phospholipid complex containing 50 wt% of bound phospholipid is shown in Figs. 1 and 2 of the previously referred to Declaration of M. Takeda. Thus, the effect of improving cholesterol metabolism can be obtained even if the protein is hydrolyzed protein, or phospholipid is enzyme-modified phospholipid, so long as the complex contain

20-50 wt% bound phospholipid or enzyme-modified phospholipid.

The Sugano article in J. Nutr. (hereinafter "first Sugano reference") discloses that undigested high-molecular-weight fraction (HMF) of soybean protein prepared after exhaustive digestion by microbial proteases significantly decreased serum cholesterol levels. This first Sugano reference described the results of a series of animal studies designed to examine the active component of the undigested fraction of soybean protein; and reports the results that the HMF obtained after peptic

digestion is as effective as that obtained after microbial protease digestion in preventing the elevation of cholesterol in serum and liver by dietary cholesterol through interference with steroid absorption. Note the paragraph bridging the right-hand and left-hand columns on pages 983 and 984 of this article.

The article by Sugano, et al. in Atherosclerosis (hereinafter "second Sugano reference") discloses how soybean derived peptides which are resistant to bacterial proteases and relatively abundant in hydrophobic amino acids exert a substantial hypocholesterolemic effect in rats compared to the parent protein. This second Sugano reference discloses that in feeding rats undigested high molecular fraction of the soybean protein, not only serum but also liver cholesterol levels were similar to those usually encountered in rats given diets free of cholesterol. Note the Summary on the first page of the second Sugano reference. Note also the Discussion beginning on page 120 of this reference, and in particular the first paragraph of this Discussion.

It is respectfully submitted that neither of the Sugano, et al. articles would have disclosed, or would have suggested, administering soybean protein together with phospholipids, much less the complex having 20-50 wt% bound phospholipid, as in the present claims, or advantages thereof as discussed in the foregoing and as shown by the evidence of record.

It is respectfully submitted that the additional teachings of Imaizumi, et al. would not have rectified the deficiencies of either of the first or second Sugano references, such that the presently claimed invention as a whole would have been obvious to one of ordinary skill in the art.

Imaizumi, et al. reports on a study carried out to determine if dietary egg yolk phospholipid also exerts a hypocholesterolemic action in rats given a high cholesterol diet, and if this action is influenced by the constituent fatty acids. The egg yolk phospholipid suppressed the elevation of serum cholesterol irrespective of its fatty acid composition, while purified phosphatidylcholine had no effect, suggesting that the ethanolamine portion is responsible for the hypocholesterolemic effect. This article goes on to state that the results found indicate that the hypolidemic effect of dietary egg yolk phospholipid can be modulated by the combination of the constituent fatty acids as well as the base moieties. See page 2469 of this article.

It is respectfully submitted that this article, either alone or in combination with either of the two Sugano references, would have neither disclosed nor would have suggested that a combination of soybean protein and phospholipid together would have an effect on cholesterol. For example, these references do not disclose, nor would have suggested, any effect of the protein and phospholipid on each other, for example, as interfering with each of their effects separately on cholesterol. Moreover, there is the following description at page 984, right-hand column, lines 16-21 of the first Sugano reference.

> In addition, because the content of lipids originating from HMF is less than 3% in the diet, the surprising hypocholesterolemic effect of HMF cannot be attributed to the lipid component alone. Rather, it is plausible that the nitrogen components in HMF-E are responsible for its activity. [*Footnote omitted. Emphasis added.*]

Furthermore, it is respectfully submitted that these references

clearly do not disclose, nor would have suggested, the complex as in the present claims, especially with amount of bound phospholipid, and advantages thereof as discussed in the foregoing.

The contention by the Examiner in the paragraph bridging pages 3 and 4 of the Office Action mailed February 20, 2004, that in Sugano there is nothing to indicate that the phospholipid is not in association with the protein (complex) is noted. As can be appreciated, the present claims recite a complex, with the phospholipid bound in the complex. Thus, reference by the Examiner to an "association with the protein" is not relevant to the presently claimed subject matter.

The additional contention by the Examiner that the claims do not define the term "complex" is noted. It is respectfully submitted that the term "complex" has a definite meaning in chemistry, which must be considered. In any event, it is respectfully submitted that the present claims recite that the phospholipid is bound in the complex, and the present claims further define what is meant by "bound". Clearly, the teachings of the applied references do not disclose, nor would have suggested, the bound phospholipid in the complex, or for that matter, use of a complex (as compared with, for example, a mixture), and advantages thereof as discussed in the foregoing.

Sirtori, et al. discloses a low-lipid diet with textured soy proteins containing 6% of lecithin (L-TVP). The article reports on the activity of this lecithinated product within a formal protocol in a multicenter study on type IIA patients, given both a complete and partial substitution of animal proteins in their diet. See the first paragraph in the left-hand column on page 349. This article goes on to disclose that

in several studies, substitution of animal proteins with a textured vegetable protein product exerted a marked hypocholesterolemic activity in type II patients; and that in the study reported in the article, similar findings were obtained with a textured vegetable protein product containing 6% by weight of lecithin. Note the "Discussion" starting on page 353 of this article.

It is respectfully submitted that Sirtori, et al. does not disclose, nor would have suggested, complexes as in the present claims; and in fact would have taught away from complexes containing amounts of bound phospholipid as in the present claims in its disclosure of textured soy proteins containing 6% of lecithin.

It is respectfully submitted that the additional teachings of Williams, et al. would not have rectified the deficiencies of Sirtori, et al., such that the presently claimed invention as a whole would have been obvious to one of ordinary skill in the art. This article reports on a proposal that intravenously injected lecithin forms circulating liposomes, and would take up cholesterol from many sources, including the arterial wall; and that, in this way, lecithin liposomes become carriers of endogenous cholesterol, these liposomes being gradually removed from circulation by the liver which catabolizes liposomes and excretes their cholesterol. Note the second paragraph on page 417; see also the paragraph bridging pages 419 and 420.

Even assuming, arguendo, that the teachings of Williams, et al. were properly combinable with the teachings of Sirtori, et al., such combined teachings would have neither disclosed nor would have suggested the presently claimed subject matter, including wherein a complex of protein and phospholipid, or protein hydrolyzate and

phospholipid were administered, the complex containing 20-50 wt% of bound phospholipid, and advantages thereof as discussed in the foregoing.

Contentions by the Examiner in connection with Sirtori, et al., in the paragraph bridging pages 5 and 6 of the Office Action mailed February 20, 2004, are noted. Here also, the Examiner does not even allege that Sirtori, et al. discloses complexes, the Examiner alleging that Sirtori, et al. indicates that lecithin "is associated with" the protein. Clearly, Sirtori, et al., either alone or in combination with the teachings of Williams, et al., would have neither taught nor would have suggested the complex as in the present claims.

Moreover, Sirtori, et al., either alone or in combination with the teachings of Williams, et al., would have neither disclosed nor would have suggested amount of phospholipid in bound form as in the present claims, and the advantages thereof.

The contention by the Examiner in the paragraph bridging pages 5 and 6 of the Office Action mailed February 20, 2004, that a review of the results in Table 2 of Applicants' specification (on page 9 thereof) "indicates no significant difference between group 2 values wherein the rats were fed 0.8% phospholipid in bound form and 20% phospholipid in free form and group 3 values wherein the rats were fed 20% bound phospholipid and 1% free cholesterol" is respectfully traversed. As is clear on page 10, lines 8-13 of Applicants' specification, Test Groups 3 and 4 showed higher arteriosclerosis index as compared with Test Groups 1 and 2, which indicates that the cholesterol metabolism in serum was improved in Test Groups 3 and 4; and Test Groups 3 and 4 also showed lower total cholesterol concentration in liver as compared with Test Groups 1 and 2. Clearly Table 2 shows unexpectedly better results achieved according to the present invention.

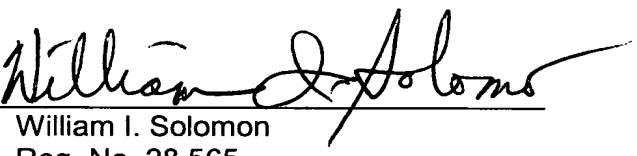
In view of the foregoing comments and amendments, entry of the present amendments, and reconsideration and allowance of all claims being considered on the merits in the above-identified application, are respectfully requested.

If the Examiner believes that there are any other points which may be clarified or otherwise disposed of either by telephone discussion or by personal interview, the Examiner is invited to contact Applicants' undersigned attorney at the number indicated below.

To the extent necessary, Applicants petition for an extension of time under 37 CFR 1.136. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to the Antonelli, Terry, Stout & Kraus, LLP Deposit Account No. 01-2135 (Docket No. 506.35379CC2), and please credit any excess fees to such Deposit Account.

Respectfully submitted,

ANTONELLI, TERRY, STOUT & KRAUS, LLP

By 
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